REMARKS

Examination of claims 1-7 is reported in the present Office Action. Claims 1-7 were rejected under 35 U.S.C. § 112, first paragraph (enablement and written description); claims 1-6 were rejected under 35 U.S.C. § 102(a); claims 1, 2, and 4 were rejected under 35 U.S.C. § 102(b); and claim 3 was rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed below. First, applicants note that, as was required by the Examiner, the hyperlinks on page 10 of the application have been deleted from the application.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-7 were rejected under § 112, first paragraph for lack of enablement. This rejection is respectfully traversed.

The Examiner first refers to applicants' definition of "titin gene," which includes nucleic acid molecules that encode proteins that have as low as 45% identity to the sequences of human or zebrafish titin proteins. The Examiner states that the term "titin gene" in the claims, thus, includes mutants, allelic variants, and homologs of titin from any source, and that such molecules have not been taught in the specification. This basis for the rejection under § 112, first paragraph has been met by the present amendment to claim 1, which now states that the titin gene that is analyzed in the claimed method is a naturally occurring titin gene. Support for this amendment can be found throughout the specification, for example, at page 2, lines 5-11, where it is stated that the invention includes a method for determining whether a test subject has or is at risk of developing a titin-related disease or condition, by analyzing a nucleic acid molecule of a sample from the test subject. Additional support for this amendment can be found, for example, on page 3, where it is stated that a "titin nucleic acid molecule" is a nucleic acid molecule that encodes a

titin polypeptide (lines 22-24), and that a "polypeptide" is a chain of two or more amino acids constituting all or part of a naturally or non-naturally occurring polypeptide (lines 6-9).

The Examiner also notes that the phrase "titin related disease or condition" is defined in the specification as including any disease or condition that is characterized by inappropriate levels of titin expression or a mutation that alters the biological activity of titin, but that the only mutation described in the specification is one that was found in a zebrafish with a weak heartbeat. This basis for the present rejection has also been met by the amendment to claim 1, by which the claim now specifies that the titin-related disease or condition is a disease or condition of the heart.

The Examiner further states that the precise locus of the pickwick mutation is not provided in the specification and, thus, that the term "pickwick mutation" has been interpreted as including any mutation that is responsible for the pickwick phenotype. The Examiner further states that the teaching of only a single mutation that is associated with a weak heartbeat in zebrafish is insufficient to provide those of skill in the art with a basis for correlating that any substitution, deletion, or insertion in the titin gene would result in a any disease or condition, including heart failure. The Examiner thus concludes that it would require undue experimentation to practice the claimed invention, because it would required a large study including subjects with a large number of diseases or conditions, and that it is unpredictable which mutations would have an effect. Applicants respectfully disagree with this basis for the rejection.

Applicants first note that, as is stated above, the claims have been amended to specify that the diseases or conditions that are diagnosed using the methods of the invention are diseases or conditions of the heart. Second, applicants respectfully submit that analysis of the sequences of

titin genes from patients and the correlation of any detected mutations with a disease or condition of the heart would not require undue experimentation. This is shown, for example, in the Satoh paper (Biochem. Biophys. Res. Com. 262:411-417, 1999), which was cited in the rejection under § 102 (a) (see below). In particular, Satoh analyzed the sequences of titin genes from eighty-two patients and identified a mutation in a titin gene that correlated with hypertrophic cardiomyopathy. All that was required to achieve this was PCR analysis of a blood sample from each of the patients, gel fractionation of the PCR products, and sequencing of any products having aberrant sizes, as compared to controls. Thus, Satoh shows that analysis of titin gene sequences of numerous subjects, using standard methods, could be carried out to identify mutations associated with heart disease, and that such analysis would not require undue experimentation.

Further support for the fact that carrying out the methods of the present claims would not have required undue experimentation can be found in the Itoh-Satoh et al. (Biochem. Biophys. Res. Com. 291:385-393, 2002) paper cited by the Examiner. In particular, this paper describes a study in which the occurrence of dilated cardiomyopathy (DCM) was correlated with three mutations in the titin gene. The Examiner notes that Itoh-Satoh found that one titin polymorphism identified in a DCM patient was also present in healthy control subjects (Arg328Cys). This does not negate the fact that detection of mutations in titin can be correlated with diseases and conditions of the heart without undue experimentation, because it was simple for Itoh-Satoh to determine the relevance of this mutation to DCM by analysis of control sequences.

Applicants respectfully request that the rejection under § 112, first paragraph for lack of enablement be withdrawn, because it would not have required undue experimentation for those

of skill in this art to determine whether a patient has a titin-related disease or condition of the heart by analysis of their titin gene sequences, as is discussed above.

Claims 1-7 were also rejected under § 112, first paragraph for lack of written description. This rejection is respectfully traversed.

The Examiner first states that the term "titin gene," as defined in the specification, includes proteins that have as little as 45% sequence identity to the human or zebrafish titin protein, and thus that this term includes mutants, allelic variants, and homologs, from any source, that have not been described in the specification, which describes only a single mutation. The Examiner thus concludes that the specification provides insufficient written description of the genus of titin genes or mutations that are encompassed by the claims.

In response, applicants first note that claim 1, from which the other rejected claims depend, has been amended to specify that the titin gene that is analyzed using the claimed methods is a naturally occurring titin gene. Applicants also note that the present claims are drawn to methods of diagnosing diseases or conditions of the heart by detection of mutations in titin genes, and not to mutant titin genes themselves. These methods certainly are adequately described in the specification, which describes obtaining samples from patients and analysis of titin sequences in the samples. It is not necessary for the specification to list every possible mutation that could be associated with these diseases or conditions, as they can easily be identified by comparison with sequences from healthy controls (see above).

The Examiner also states in this rejection that a description of how to isolate a sequence is not sufficient for satisfying the written description requirement, and that the nucleic acid itself is required, but these statements are not relevant to the present claims. Rather, these statements would be more appropriate in a rejection of claims to nucleic acid molecules or proteins

themselves, not to methods that involve the detection of mutations. Applicants clearly describe the steps required for carrying out their method, and also provide reference sequences (e.g., human titin). Applicants thus have clearly shown that they invented what is claimed, and this rejection should therefore be withdrawn.

Rejection under 35 U.S.C. § 102(a)

Claims 1-6 were rejected under § 102(a) as being anticipated by Satoh et al. (Biochem. Biophys. Res. Com. 262:411-417, 1999). Applicants request that this rejection now be withdrawn because, as is stated in the accompanying Declaration of inventor Xiaolei Xu, applicants established a connection between a mutation causing a weak heartbeat and the titin gene, and thus reduced the present invention to practice, prior to the publication date of the Satoh reference.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 2, and 4 were rejected under § 102(b) as being anticipated by Jäckel et al. (FEBS Letters 408:21-24, 1997). Jäckel describes the detection of a mutation in the titin gene of BHK-21-Bi cells. Jäckel does not mention obtaining a sample from a test subject, as is required by the present claims. This rejection thus can now be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claim 3 was rejected under § 103(a) for obviousness over Jäckel (FEBS Letters 408:21-24, 1997). This claim specifies that the method of claim 1 includes the step of sequencing titin nucleic acid molecules from the tested subject. The Examiner states that even though Jäckel

employs Southern blot analysis to analyze their mutation, it would have been obvious to employ sequencing instead, because sequencing methods were well known and those of skill in the art would have known that sequencing is an effective approach to identifying mutations. This rejection is respectfully traversed.

Claim 1, from which claim 3 depends, is drawn to a method for diagnosing a disease or condition of the heart in a human by detection of mutations in titin sequences of the human. Jäckel, as is noted above, describes the identification of a titin mutation in a cell line. Jäckel nowhere mentions detection of titin mutations in humans, and provides no motivation to do so, as Jäckel provides no indication that titin mutations could bear any relationship to any human disease or condition, not to mention a disease or condition of the heart. The rejection over Jäckel should therefore be withdrawn.

Claim 3 was also rejected under § 103(a) for obviousness over Jäckel, in view of Satoh. As is discussed above, Satoh is not prior art to the present claims. Thus, in only being supported by Jäckel, this rejection is identical to the previous rejection, and thus should be withdrawn for the same reasons discussed above.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: December 3, 2002

Susan M. Michaud

Susan M. Michaud, Ph.D.
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045
00786.381002 reply to first office action.doc

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Version of Amendment with Markings to Show Changes Made

The paragraph spanning pages 9-10 of the specification has been amended as follows.

Titin nucleic acid molecules, polypeptides, and antibodies can be used in methods to diagnose or to monitor diseases and conditions involving mutations in, or inappropriate expression of, *titin* genes. As discussed further below, the *pickwick* mutation in zebrafish, which is present in the *titin* gene, is characterized by a phenotype that is similar to that of heart failure in humans. Thus, detection of abnormalities in *titin* genes or their expression can be used in methods to diagnose, or to monitor treatment or development of, human heart disease, such as heart failure. For use as references, the human cardiac *titin* cDNA sequence is presented herein as [can be found at: http://www.embl-heidelberg.de/ExternalInfo/Titin/cardiacseq.html (]SEQ ID NO:1[)], while the corresponding protein sequence is presented herein as [can be found at: http://www.embl-heidelberg.de/ExternalInfo/Titin/cardiacpep.html (]SEQ ID NO:2[)].

Claim 1 has been amended as follows.

1. (Amended) A method of determining whether a test subject has, or is at risk of developing, a titin-related disease or condition of the heart, said method comprising obtaining a sample from said test subject and analyzing a nucleic acid molecule of [a] said sample [from the test subject] to determine whether the test subject has a mutation in a naturally-occurring *titin* gene, wherein the presence of said mutation is an indication that said test subject has, or is at risk of developing, a titin-related disease of the heart.

Pending Claims After Entry of Amendment

1. (Amended) A method of determining whether a test subject has, or is at risk of developing, a titin-related disease or condition of the heart, said method comprising obtaining a sample from said test subject and analyzing a nucleic acid molecule of said sample to determine whether the test subject has a mutation in a naturally-occurring *titin* gene, wherein the presence of said mutation is an indication that said test subject has, or is at risk of developing, a titin-related disease of the heart.

2. The method of claim 1, further comprising the step of using nucleic acid molecule primers specific for the *titin* gene for nucleic acid molecule amplification of the *titin* gene by the polymerase chain reaction.

3. The method of claim 1, further comprising the step of sequencing *titin* nucleic acid molecules from said test subject.

4. The method of claim 1, wherein said test subject is a mammal.

5. The method of claim 1, wherein said test subject is human.

6. The method of claim 1, wherein said disease or condition is heart failure.